

# EXHIBIT

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QUINTILES

Quintiles, Inc.  
Post Office Box 9708  
Kansas City, MO 64134-0708  
(816) 767-6000

June 3, 2002

Central Document Room  
Center for Drug Evaluation and Research  
Food and Drug Administration  
12229 Wilkins Avenue  
Rockville, MD 20852

**Subject:** **Investigational New Drug Application  
BSF 208075 for Pulmonary Arterial Hypertension** **Serial No. 000  
(Initial Submission)**

Dear Sir or Madam:

On behalf of Myogen, Inc., Quintiles, Inc. is submitting with this correspondence an initial Investigational New Drug Application (IND) for a new chemical entity, BSF 208075, an ETA selective endothelin receptor antagonist, being investigated in patients with pulmonary arterial hypertension. In accordance with 21 CFR Part 312 this thirty volume IND is submitted in triplicate.

To aid in the evaluation of the application, Section 10 of this IND contains additional information regarding communication with the Division of Cardio-Renal Drug Products that took place previously under IND 63,412. This includes a summary of the actions taken by Myogen in response to the Division's recommendations and copies of correspondence and meeting minutes that discussed the investigation of BSF 208075 for the indication of pulmonary arterial hypertension. In addition, Section 11 of this IND contains a copy of the informed consent form for protocol AMB-220, which is submitted in Section 6.

Also, please find enclosed for submission a letter from Myogen, Inc. transferring the responsibility as US Agent and Authorized Representative to Quintiles, Inc.; a letter from Quintiles accepting the transfer of responsibility; and an official Transfer of US Regulatory Obligations form delineating the duties being transferred.

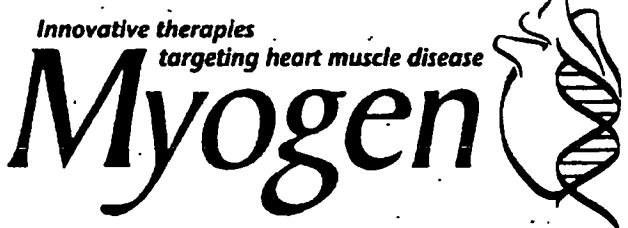
Any questions concerning this Investigational New Drug Application should be directed to:

Marguerite Enlow, Pharm.D., RAC  
Associate Regulatory Director,  
Regulatory and Technical Services  
Quintiles, Inc.  
P.O. Box 9708  
Kansas City, MO 64134-0708  
Telephone: (816) 767-6408  
Fax: (816) 767-7373

Sincerely,

  
Cynthia Kirk, Ph.D., RAC  
Executive Director  
Regulatory and Technical Services  
Quintiles, Inc. Kansas City

June 3, 2002



Douglas Throckmorton, M.D.  
Director, Division of Cardio-Renal Drug Products  
Center for Drug Evaluation and Research (HFD-110)  
Food and Drug Administration

**Subject: BSF-208075  
Selective Endothelin Receptor Antagonist  
For Pulmonary Arterial Hypertension**

**General Correspondence:  
Transfer of responsibility as  
US Agent and Authorized  
Representative**

Dear Dr. Throckmorton:

Effective June 3, 2002, Myogen, Inc. is authorizing Quintiles, Inc., Kansas City, MO to act as its U.S. Agent and Authorized Representative for BSF 208075, an ETA Selective Endothelin Receptor Antagonist, being investigated in patients with pulmonary arterial hypertension. The duties to be performed by Quintiles, Inc. are:

- Submission of the IND
- Verbal and written interaction with the FDA
- Conduct of meetings with the FDA
- Submission of the IND annual reports
- Submission of IND amendments
- General IND maintenance

The contact person at Quintiles, Inc., is:

Marguerite Enlow, Pharm.D., RAC  
Associate Regulatory Director,  
Regulatory and Technical Services  
Quintiles, Inc.  
P.O. Box 9708  
Kansas City, MO 64134-0708  
Telephone: (816) 767-6408  
Fax: (816) 767-7373

If you have any questions regarding the above information, please do not hesitate to contact me at Myogen, Inc., 7577 West 103rd Ave. #212, Westminster, CO 80021-5426, telephone (303) 464-5221.

Sincerely,

J. William Freytag  
President, CEO and Chairman  
Myogen, Inc.



Quintiles, Inc.  
Post Office Box 9708  
Kansas City, MO 64134-0708  
(816) 767-6000

June 3, 2002

Douglas Throckmorton, M.D.  
Director, Division of Cardio-Renal Drug Products  
Center for Drug Evaluation and Research (HFD-110)  
Food and Drug Administration

**Subject:** BSF 208075  
Selective Endothelin Receptor Antagonist  
For Pulmonary Arterial Hypertension

**General Correspondence:**  
Acceptance of responsibility  
as US Agent and Authorized  
Representative

Dear Dr. Throckmorton:

Effective June 3, 2002, Quintiles, Inc., Kansas City, MO assumes the responsibility from Myogen, Inc. as the U.S. Agent and Authorized Representative for BSF 208075, an ETA Selective Endothelin Receptor Antagonist, being investigated in patients with pulmonary arterial hypertension. The duties to be performed by Quintiles, Inc. are:

- Submission of the IND
- Verbal and written interaction with the FDA
- Conduct of meetings with the FDA
- Submission of the IND annual reports
- Submission of IND amendments
- General IND maintenance

The contact person at Quintiles, Inc., is:

Marguerite Enlow, Pharm.D., RAC  
Associate Regulatory Director,  
Regulatory and Technical Services  
Quintiles, Inc.  
P.O. Box 9708  
Kansas City, MO 64134-0708  
Telephone: (816) 767-6408  
Fax: (816) 767-7373

If you have any questions regarding the above information, please do not hesitate to contact me at Quintiles, Inc., P.O. Box 9708, Kansas City, Missouri 64134-0708, telephone (816) 767-6493.

Sincerely,

A handwritten signature in black ink, appearing to read 'Cynthia Kirk'.

Cynthia Kirk, Ph.D., RAC  
Executive Director  
Regulatory and Technical Services  
Quintiles, Inc. Kansas City

TRANSFER OF US FDA REGULATORY OBLIGATIONS FOR INVESTIGATIONAL  
PHARMACEUTICAL AND BIOLOGIC PRODUCTS UNDER AN INVESTIGATIONAL NEW DRUG (IND)  
APPLICATION (21 CFR 312.52)

Form No: CRO.FM.AMR.RA002.V02

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Sponsor:	Myogen	Project Code/ Work Order Number:	Not Assigned
Product Name:	BSF 208075	IND Number:	Not Available
Indication:	Pulmonary Arterial Hypertension	Protocol Number:	All protocols

Responsibility	21 CFR Reference	Obligation Assigned to:	
		Sponsor	Quintiles
A. 1. Preparation of all or part of an IND application	312.23	X	X
2. Submission of IND application to FDA		<input type="checkbox"/>	X
B. Maintain an IND with the following amendments, as necessary:			
1. Preparation of Protocol amendments (includes new protocols, changes in protocols, adding new investigators)	312.30	X	<input type="checkbox"/>
2. Preparation of Chemistry, Manufacturing, and Control amendments	312.31	X	<input type="checkbox"/>
3. Preparation of Pharmacology and Toxicology amendments	312.31	X	<input type="checkbox"/>
4. Preparation of Clinical amendments	312.31	X	<input type="checkbox"/>
5. Safety Reports	312.32	<input type="checkbox"/>	<input type="checkbox"/>
(a) Preparation of initial report		X	<input type="checkbox"/>
(b) Preparation of follow-up reports		X	<input type="checkbox"/>
(c) Notifications to FDA (phone/fax or written)		<input type="checkbox"/>	X
(d) Notifications to investigators		X	<input type="checkbox"/>
6. Preparation of Annual Reports	312.33	X	X
7. Preparation of response to request for information or clinical hold	312.41, 42	X	X
8. Preparation of letter to withdraw an IND	312.38	X	X
9. Act as IND agent; submit all amendments to FDA	312.23 - 42	<input type="checkbox"/>	X
C. Selecting investigators and monitors	312.53		
1. Select qualified investigators <sup>1</sup>	312.53 (a)	X	<input type="checkbox"/>
2. Control of drug <sup>1</sup>	312.53 (c)	X	<input type="checkbox"/>
(a) Approve drug shipment after review of required information from investigator (including signed Form FDA 1572, CV)			
(b) Ship drug to approved investigators	312.53 (b)	<input type="checkbox"/>	X
3. Provide qualified monitors <sup>1</sup>	312.53 (d)	X	<input type="checkbox"/>

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4. Informing investigators <sup>1</sup>				
(a) Review with investigators their regulatory responsibilities	312.60 -.69	X	<input type="checkbox"/>	
(b) Supply investigator's brochure	312.55 (a)	X	<input type="checkbox"/>	
(c) Inform investigators of new safety information about the study drug	312.55 (b)	X	<input type="checkbox"/>	
<b>D. Review of ongoing investigations</b>	<b>312.56</b>			
1. Monitoring the investigation (includes ensuring that investigator is complying with all commitments in Section 9 of the signed Form FDA-1572) <sup>1</sup>	312.56(a)	X	<input type="checkbox"/>	
2. Discontinue investigator participation if not compliant <sup>1</sup> Note: If the sponsor does not discontinue an investigator who Quintiles believes to be significantly non-compliant, Quintiles will request a complete transfer of regulatory obligation for that site back to the sponsor.	312.56(b)	X	<input type="checkbox"/>	
3. Initial evaluation of all adverse events <sup>1</sup>	312.56 (c)	X	<input type="checkbox"/>	
4. Upon discontinuation of a study <sup>1</sup> :	312.56 (d)	<input type="checkbox"/>	X	
(a) Notify FDA		X	<input type="checkbox"/>	
(b) Notify IRBs and investigators		X	<input type="checkbox"/>	
(b) Assure disposition of drug from sites to sponsor		X	<input type="checkbox"/>	
<b>E. Recordkeeping and record retention</b>	<b>312.57</b>			
1. Maintain sponsor records and reports for 2 years after study end <u>or</u> marketing application approved, for	312.57(a)(b)			
(a) Records of drug shipment and disposition		X	<input type="checkbox"/>	
(b) All correspondence with sponsor, FDA, IRB, investigators		X	<input type="checkbox"/>	
(c) Records concerning adverse effects		X	<input type="checkbox"/>	
(d) Other records required by FDA		X	<input type="checkbox"/>	
2. Retain reserve samples of test articles and reference standards used in bioequivalence or bioavailability studies	312.57 (c)	X	<input type="checkbox"/>	
<b>F. Disposition of unused supply of investigational drug</b>	<b>312.59</b>			
1. Assure return of drug from site to sponsor <sup>1</sup>		X	<input type="checkbox"/>	
2. Conduct final disposition or destruction of drug <sup>1</sup>		X	<input type="checkbox"/>	
<b>G. If requested by FDA, submission of sponsor's records and reports to FDA for inspection</b>	<b>312.58 (a)</b>	X	<input type="checkbox"/>	
<b>H. Apply for FDA approval to export investigational drug if:</b>	<b>312.110</b>	<input type="checkbox"/>	<input type="checkbox"/>	
(a) Drug is not approved for marketing in any country, AND				
(b) Drug is not under an active IND, AND				
(c) Drug is not being exported to one of listed countries <sup>2</sup>				
X Not applicable				
<b>I. Represent sponsor in resolution of disputes with FDA</b>	<b>312.48</b>	X	<input type="checkbox"/>	
<b>J. Obtain investigator financial disclosure information</b>	[FR 2/2/98]	X	<input type="checkbox"/>	

Sponsor's name  
Project code

TRANSFER OF US FDA REGULATORY OBLIGATIONS FOR INVESTIGATIONAL  
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<sup>1</sup> If responsibility for an item is shared between the sponsor and Quintiles, both boxes will be checked. Quintiles' responsibility for the item is limited to the list of sites attached to this document. This must be confirmed in the contract.

<sup>2</sup> Listed countries: Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, and current member nations of the European Union and European Economic Area.

According to 21 CFR 312.52(b), "A contract research organization that assumes any obligation of a sponsor shall comply with the specific regulations in this chapter applicable to this obligation and shall be subject to the same regulatory action as a sponsor for failure to comply with any obligation assumed under these regulations." The assignment of responsibility does not preclude either the sponsor or the CRO from participating in the requirements of the CFR.

The sponsor hereby transfers to Quintiles, Inc. the responsibilities indicated above under the column titled "Obligation Assigned to QUINTILES," effective Jan 18 2002 (date).

Sponsor: MYOGEN

J. William Freytag  
Signature

J. William Freytag  
Printed Name

President, CEO and Chairman

Title

1-10-02  
Date

QUINTILES

Marguerite Enlow, Ph.D.  
Regulatory & Technical Services Signature

Marguerite Enlow  
Printed Name

Associate Director

Title

1/18/02  
Date

Sponsor's name  
Project code